The Purvis Oration

ON

SOME POINTS IN THE DIAGNOSIS AND TREATMENT OF GRANULAR KIDNEY

Delivered before the West Kent Medico-Chirurgical Society

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Mr. President and Gentlemen,—The list of distinguished men who have preceded me as Purvis Orators shows what a great compliment it is to be invited to deliver this oration. I appreciate the honour very highly, and I trust that the contribution of to-night will not fall short of the standard set by my predecessors.

Dr. Purvis, in whose honour this oration was established, was a practitioner of wide experience, to whom the clinical side of medicine would most forcibly appeal, and in casting about for a subject I tried to select one which I thought would have met with his approval. Granular kidney seemed to me such a subject. It is a common disease, the interest of which is ever new, for it is constantly appearing in unexpected shapes, prepares for us many surprises, is by no means rarely overlooked, and presents many points of theoretical interest and of practical importance which may be worthy of our consideration. Although in the later stages the disease is past cure, still by an early diagnosis I believe much may be done to minimise its gravity, diminish its risks, and delay its progress.

Etiology.

Granular kidney is an entity. It is a true disease, for it has definite morbid lesions, and definite

clinical signs associated with them, which render diagnosis easy during life.

Shrunken kidneys were long known and described, but it was not until Gull and Sutton wrote that this affection was recognised as a disease. They drew attention to the changes in the blood-vessels and heart which were associated with the renal lesions, and gave the disease the name of "arterio-capillary fibrosis." Since then discussion has never ceased to rage as to the relation between the vascular and renal changes. The possible relation is threefold: (1) the renal changes may be primary, and lead to the vascular; (2) the vascular may be primary, and the renal secondary; or (3) both the renal and vascular changes may be joint results of some common cause. In spite of more than 40 years' discussion the problem is still unsettled.

Granular kidney is the best name for the disease, for it is the one generally accepted and best understood. Granular kidneys would be more accurate, for both kidneys are always affected and to a similar degree. The lesions are symmetrical and bilateral, never unilateral or local. This symmetry may be used as an argument in favour of some general cause to which the vascular and renal lesions alike are due, and there is the analogy of peripheral neuritis to support it. For peripheral neuritis, if bilateral, is always due to some general cause of a toxic character, like poisoning by alcohol or arsenic; whereas if it be unilateral, it is the result of some local cause. All local affections of the kidney, whether leading to shrinking or not, may be at once cut off, for there is not such a thing as granular kidney in which one kidney alone is affected.

Granular kidney is a form of chronic interstitial nephritis, yet all forms of chronic interstitial nephritis, even if bilateral, are not granular kidney. For instance, the gouty kidney, so-called, is a mixture of interstitial fibrosis with cell degeneration, yet gout has nothing essentially to do with granular kidney, for even in long-standing gout the kidneys need not be granular, nor is gout more than an accidental—i.e., not a necessary—accompaniment of granular kidney.

Clinical Evidence and Morbid Anatomy.

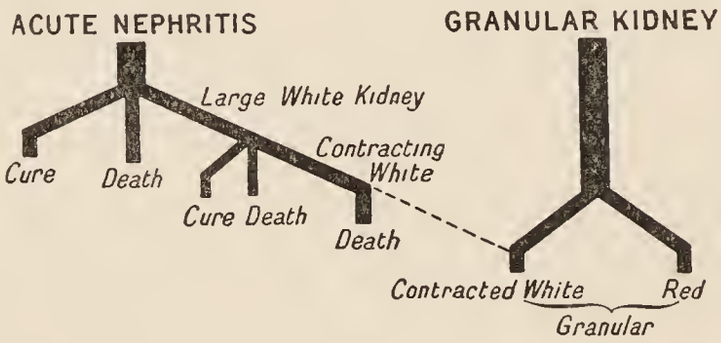
Both gout and lead are frequently given as causes of granular kidney. They are not infrequently associated with it, yet the true relation is probably the contrary to that suggested, the patients being especially liable to these affections, because their kidneys are granular and elimination defective, so that they are not causes of granular kidney, but its consequences.

Granular kidneys are usually small, but not necessarily, for they may be large and considerably above normal weight. Just as in alcoholic hepatic cirrhosis the liver may be large or small—i.e., above or below normal weight—so may granular kidneys. Renal cirrhosis would not be a bad name if it were understood that the whole of the renal organ—i.e., both kidneys—must be involved, as is the whole liver.

Two forms of granular kidney are described, the *contracted white* and the *contracted red*, and it is suggested that the difference in colour connotes a difference in cause, the white being the result of past inflammation and the red not. If this were so it ought to be capable of easy proof. Acute nephritis may certainly as a pathological process lead to interstitial change and some fibrosis, and in the end it may be to extreme wasting and contraction —i.e., to granular kidney; but if this often happened there ought to be no lack of clinical proof of it, for acute nephritis is a common affection enough, and its symptoms are too obvious to be overlooked. Yet clinical evidence is strikingly defective; I have looked for it for years, and have not seen a single clinical case which I could regard as conclusive, though I have met with many that pointed to an opposite conclusion. The two forms of granular kidney, the contracted white and the contracted red, are about equally common in the post-mortem room. If the contracted white kidney be as common as this, and the theory stated be true, the history of antecedent acute nephritis ought to be frequently obtained, and yet it is not.

It is impossible during life, either from the clinical history or symptoms, to forecast with

probability whether the kidney will be white or red. There is, of course, the same chance of guessing rightly as there is in tossing a halfpenny, but no more. I do not believe, therefore, that there is any difference between the contracted white and the contracted red granular kidney except the accidental one of colour. The suggestions of morbid anatomy must be in harmony with clinical experience. The clinical evidence in this question is utterly against the theory. The conclusion is unavoidable that the theory is wrong. The diagram shows the difference in theory and the dotted line where the clinical evidence is lacking.



If there is little evidence to prove that acute nephritis leads to granular kidney there is plenty to prove the converse. It is common enough for an adult to come under observation with the first attack of acute nephritis in which the condition of the heart and vessels and even advanced changes in the retina show conclusively that the kidneys are granular and of date long antecedent to the onset of the acute nephritis. The correct conclusion seems to be that acute nephritis in the adult frequently occurs because the kidneys are already unsound.

Symptoms.

Granular kidney is often overlooked because there are for a long time no symptoms at all, or if there are any they are misleading and point to almost any part of the body rather than to the kidneys. Yet so soon as granular kidney is thought of the diagnosis becomes clear, and all difficulty in

interpreting the symptoms vanishes. It is generally the pulse that gives the clue, for so soon as the finger is placed upon the radial the characteristic thickening of the artery and the increased tension raise at once the question of granular kidney, and further examination soon makes the diagnosis certain. As compared with the thickening of the arterial wall and the increased tension in it the character of the pulse wave is unimportant.

The characteristic symptoms of granular kidney are: (1) the arterial thickening; (2) the increased arterial tension; (3) the characters of the urine; (4) the hypertrophy of the heart; and (5) the retinal changes. Upon each of these I have a few remarks to make.

Arterial Thickening.

Arterial sclerosis is a term which leads to much confusion, for as a general term it is a mere translation, and indicates nothing as to the nature of the thickening or its causes. But as a special term it is often used to denote that form of arterial thickening met with in granular kidney. The use of the same term in both a general and a special sense tends to confusion, and it would be well if the term could be eliminated from our terminology altogether.

Dr. F. W. Andrewes[1] has recently published an important report upon the forms of arterial change as met with in the post-mortem room. The monograph is of special importance as showing how common such changes are, and how widespread and advanced they may be without giving any definite symptoms by which they can be recognised during life. Many of these lesions are not associated with appreciable thickening of the walls, and do not, therefore, concern us in our present consideration.

Those that are associated with thickening fall into two well-marked clinical groups.

1. The first is commonly called *atheromatous*. This is a patchy, nodular, irregular degeneration, widespread but not universal, affecting especially

[1] Report of the Medical Officer, Local Government Board, 1911–12.

the aorta itself, the cerebral vessels, and some of the middle-sized vessels, such as the radial and temporal. This is the usual degeneration of advancing life, and has been called senile. Dr. Andrewes would subdivide this group into two forms, the senile and the nodular. The *senile*, in which the changes in the media are prominent, and some degree of calcification is the rule. The *nodular*, which commences in the intima, but involves the media later, and ends in the characteristic lesions of atheroma; this may occur in earlier life. The two changes are generally combined as age advances, and so for clinical purposes may be considered together.

2. The second group is that following abnormally high blood pressures, and is especially common in chronic renal disease. It affects the media especially, which is at first hypertrophied and then becomes fibrotic, but it is associated later with changes also in the intima. A good descriptive name is wanted for this, but it is often called arterio-sclerosis.

3. The third group is syphilitic, a local gummatous change involving primarily the intima, often multiple, but not generalised, affecting the aorta and cerebral vessels especially. This does not affect the radial or temporal artery, and therefore raises no difficulty in connexion with granular kidney.

If, then, the artery at the wrist is thickened there are two chief changes to consider, the atheromatous and the renal. These may be distinguished by age. Thus in the early half of life atheroma is unlikely; while in the latter half, though atheroma is common, the renal form cannot be excluded, for granular kidney may occur at any age, even in the very young and in the aged.

In the young adult there is one form which is not often referred to, yet it is of importance. I hardly ever lecture on arterial thickening without soon seeing some fine, healthy, athletic young student who has felt his arteries, found them abnormally palpable, and has jumped to the conclusion that he

must have renal disease. In such a case the arterial thickening is not an arterial degeneration and a sign of disease, but a physiological hypertrophy and evidence of extremely vigorous life. Violent muscular effort leads to hypertophy of the muscular coat of the arteries as it does of the heart. It is most marked in the most athletic and healthy, such as gymnasts or great oarsmen, and we may assume that they would not be capable of such sustained physical effort if this hypertrophy did not occur. I am glad to draw attention to this form of thickening, as it is not so generally recognised as it ought to be. On the other hand, it must be borne in mind that a similar degree of thickening in one who is not a great athlete would be pathological. This physiological hypertrophy disappears in the artery, as it does in the heart, when the call for it is over, and leaves no trace behind. I do not know of any instance to show that arterial degeneration can be fairly referred to it.

Are the arteries invariably thickened in granular kidney, and must they necessarily be? Perhaps not. I have seen a few cases, at any rate, in which the other signs made the diagnosis certain, and yet there was no thickening of the radial sufficiently obvious to attract attention, for the thickening was not more than was compatible with the normal for that age.

The thickening in the early stage of granular kidney is largely muscular, as can be shown by the effect of nitrite of amyl, which relaxes the muscular tissue, but has no action on fibrous tissue. The thickening felt in the radial can be seen with the ophthalmoscope in the retina, where the arteries show that wide and brilliant streak to which the graphic name "silver-wire arteries" has been given. Silver-wire arteries do not occur with any other form of arterial thickening except that associated with granular kidney, and are therefore pathognomonic.

Arterial Tension.

Arterial tension is the next subject for consideration. What we require to know is the tension or pressure in the arteries *between* the pulse beats.

It is this pressure which converts the intermittent flow of blood into a constant stream, and upon which the nutrition of the tissues in large measure depends. We hear a great deal nowadays of blood pressures, but these are systolic pressures and measures of the force of the heart beat and pulse wave. The tension is not the systolic but the diastolic pressure. The systolic and diastolic pressures are often confused together, yet they ought to be kept quite distinct from one another.

The character of the pulse wave depends upon the force of the contraction of the left ventricle and the amount of blood driven into the arteries, modified by the resistance of the arterial wall and of the capillary area.

The same systolic blood pressure might give very different pulse curves. The crest would be high and the wave short if the resistance were low, and the crest low and the wave long if the resistance were high, thus producing the low, flat, long wave of the sphygmographic tracing of the so-called renal pulse.

An illustration will make my meaning clear.

A youth of 21 was suffering from advanced aortic incompetence. The systolic blood pressure was 180 mm. or more, yet the pulse was one of low tension owing to the defective nutrition and consequent loss of tone and the immediate collapse of the artery so soon as the wave had passed, owing to the regurgitation. Although the systolic blood pressure was high the diastolic tension was very low, and the patient was suffering more from low diastolic pressure than from the high systolic pressure, and to have reduced the systolic pressure by treatment would obviously have done harm.

There are many instruments which measure the systolic pressure, but none I know of which satisfactorily determines the diastolic pressure. In my opinion no instrument is yet invented which will take the place of the educated finger of the thoughtful physician.

The arterial tension in granular kidney varies. It ought to be above normal. It were better that the patient had not got granular kidney, but having granular kidney he ought to have a raised tension. With a low tension the patient is not so well, and will not be better till the pressure rises again.

There is a sort of average raised tension for granular kidney, which cannot, however, be well expressed in figures. The tension may rise above this or fall below it, and may then require appropriate treatment, but to attempt to reduce the average raised tension of granular kidney to the normal for health is a mistake and will do harm.

What is curious and not generally known is that the tension is subject to *fluctuations* of a peculiar kind, so that when the finger is on the pulse the tension is felt to rise and fall at short and irregular intervals. This is quite plain to the finger, but I have never yet succeeded, in spite of many attempts, in demonstrating it by sphygmographic tracings. I have only observed these fluctuations in the later stages of granular kidney when the patient was very ill, but they are by no means rare then.

Hyperpiesis.

Though high tension is a cardinal symptom of granular kidney, it is met with not infrequently without arterial thickening or any other evidence of granular kidney. This has been called *hyperpiesis*, and it deserves a special name, for it is a distinct clinical condition. It is met with in persons of great energy, who work and live at high tension and are not happy unless they do. They do two men's work and often two men's play as well. They live freely, yet without what can be called exactly excess. In fact, they enjoy life to the full.

The condition seems to be confined to the male sex. At any rate, I have not seen any case in a woman, even in those who lead strenuous lives. The blood pressure ranges round about 200 mm. Their life is one of high pressure; indeed, they probably could not live the life they do without a high blood pressure. High blood pressure for such persons is their normal condition, and it cannot be reduced with impunity. The most drastic measures may be employed till the health becomes seriously affected, but the blood pressure remains as high as ever. All that the treatment has done is to nake the patients unhappy and incapable of their work. The drastic treatment is given up; they return to their ordi-

nary mode of living, begin again to enjoy life, and soon are as hard at work as ever.

It can hardly be doubted that in the end such abnormal pressure will tell upon the vessels, and lead in time to some of those degenerative changes which Dr. Andrewes has described. Cardiac hypertrophy or failure may occur, or some vascular trouble develop, especially in the brain. These risks may be provided against in general ways, but not directly through the blood-pressure. The high blood pressure in their case is their normal condition, without which they would not be what they are—in popular parlance, they are built that way. Given the choice, they would rather have their high blood pressure with its risks and enjoy their life, than have their pressure lowered and lose their enjoyment of life.

The following is a typical case of this class.

A man, aged 48, about 5 ft. 10 in. in height, and weighing 13½ st., came to see me. He said he had been working very hard, felt tired, and wanted a holiday. He had taken a good one and felt now perfectly fit, but before going back he wanted to be overhauled to satisfy himself that he was all right. He was a man of fine physique and looked perfectly well. I could find nothing wrong with him except a slight increase of pulse tension. This was obvious enough. I wish I had measured it, but I did not think it necessary. He returned to work, lived his usual strenuous life, and remained perfectly well for two or three years.

Soon after that I saw him again, and I was shocked at his appearance. He was thin and anæmic, and looked like a man with malignant disease. He told me that he had lived his ordinary strenuous life till one morning six months previously. He had gone to bed well, but on rising he felt faint and giddy. The medical man, finding his blood pressure 180–200 mm., said he had had a narrow shave of apoplexy, bled him freely once or twice from the arm, and kept him in bed for some weeks upon very low diet. After a time he got up, feeling very weak and miserable For some time longer he continued with a greatly restricted diet and led an invalid life. Then finding he got worse instead of better he came to see me again.

I examined him carefully and failed to find any organic disease. The only thing abnormal beyond his appearance was the high blood pressure of 180 mm. He told me that it had been at that height all the time, and that dieting and treatment had had no effect upon it whatever. I considered him to be suffering from starvation ; I ordered him a good

dinner with some champagne. He had it and felt all the better. I advised him to continue with a liberal but plain diet. He soon picked up and looked a different being. In two or three weeks' time he was well enough to go home. I cautioned him to live at a lower rate. I heard subsequently that he had gradually resumed his ordinary way of living, though he was careful in respect of wine and tobacco, delegated as much of his work as he could, and took more frequent holidays.

Though the medical man had no doubt good reasons for his anxiety at the commencement of the patient's illness, it is clear that the lowering treatment had been continued too long until the health suffered seriously. It is interesting to know that in spite of the stringent and lowering *régime*, and the effect this had had upon the health, the effect upon the blood pressure was *nil*.

I saw the patient again two years or so later. He had been in perfect health, and was passing through London on his way home after a good holiday abroad. The weather was very hot, and he was overcome one day with what he called a faint. When I saw him there was slight weakness of the left arm which he complained of, as well as some thickness of speech, and the left side of the face was somewhat smoothed out, and moved imperfectly. He had evidently had some incomplete thrombosis of one of the subdivisions of the right Sylvian artery. In a few days he had greatly improved and was able to continue his journey to his home, which he reached safely. My account of him at present is incomplete, but I hear he is much better, though not quite well or strong enough to undertake his old work. This attack is, no doubt, the consequence of the degeneration in his arteries to which I have said the high pressure was likely to lead. The most careful examination failed throughout to give any evidence of renal disease. The arteries were not at all thickened—indeed, if anything, they were unusually thin and supple for his age.

Albuminuria.

Of albuminuria there is not much that I need say. The amount of albumin is usually small, sometimes merely a trace. The most important fact about it is that it may be absent at some time of the day or even be absent altogether for days or weeks. As a rule, however, it is persistent, and does not vary much in amount from day to day or at different times of the day.

Albuminuria is a symptom, and not a disease. It

is of importance because it ought not to be, and is a sign of something wrong. Its significance varies especially with age. In schoolboys and young adults it is common, and is then often called physiological, but physiological it cannot be, though it need not be renal. In schoolboys it is met with in two types: (1) in one the schoolboys are well developed, muscular and active, and apparently in vigorous health; and (2) in the other the boys are rather weedy, pale, or overgrown. In either case it is an affection of the age period and disappears as the boys grow up.

There is another class of the kind which has been called accidental albuminuria, and which is of importance. This is met with in athletes, university crews in training, football players, young recruits after drill—in fact, in young adults who are using their muscles violently. It disappears when the muscular effort is given up, and is not followed by any permanent mischief.

As long as albuminuria occurs as the only symptom in the young it is probably of no significance, but if it be associated with other signs, and especially with arterial thickening, even in slight degrees, more caution must be taken in pronouncing it to be of no gravity. For it may be the early state of granular kidney, for this is a disease which commences in early life and is not really rare in the quite young. Even when albuminuria is the single sign, its gravity increases with every year of age after 25, because of the increasing probability of its being due to granular kidney.

Even when a history of acute nephritis is obtained in earlier life, so that the albuminuria is in all probability due to some renal change it does not follow that the kidneys are involved to any great extent. For the acute nephritis may have resolved completely in one kidney and not in the other, or in both kidneys to a great extent—it may be of 9/10, 19/20, or 49/50. Yet the little patch of chronic mischief left will be quite sufficient to account for the amount of albumin present. In such cases the condition of the kidney must not be assumed on theoretical grounds, but must be determined by careful investigation. If there is no evidence of renal inadequacy the albuminuria may be of little

importance, and life run its ordinary course to its usual span.

As the amount of albumin lost is so small, it is too little in itself to have any effect upon the health, and if the health suffer it is the result of other causes. The albuminuria need not, therefore, be drastically treated. Moreover, the strictest dieting often produces no effect upon it, though it may have a disastrous effect upon the health. Even if the albuminuria could be made to disappear, its disappearance would not show that the disease was cured, but a useful clinical indication would have been lost. As a matter of fact, treatment in these cases has little effect or none at all. As with raised arterial tension, so with albuminuria treat it if need be, but beware of over-treatment.

Albuminuric Retinitis.

Of albuminuric or renal retinitis there are two forms—the one pathognomonic of granular kidney, the other not.

The one is *inflammatory*, and might continue to be called retinitis. It is associated with much swelling of the disc and retina, and might therefore be called *exsudative*. It is exactly the same as other forms of exsudative or inflammatory retinitis, and cannot be distinguished from them, and so it comes that mistakes in diagnosis have been made, for example, between granular kidney and cerebral tumour, especially when headache has been the prominent symptom.

The other form is *degenerative* and not inflammatory. It would be better to describe it as *renal retinal degeneration*. This is *sui generis*, and pathognomonic of granular kidney. I do not know of any retinal change like it, and when it is present granular kidney may be diagnosed with certainty.

The *acute exsudative form* is probably toxic in origin. It is met with in acute nephritis as well as in chronic. In acute nephritis it may resolve and completely disappear, leaving no defects of vision behind. In chronic nephritis it is more serious, and does not as a rule resolve because the renal condition has got beyond the stage of recovery.

There is no relation between the two forms, and it is not true to speak of the exsudative form as a later stage of the degenerative. They are distinct conditions, associated sometimes together, and due to different pathological conditions.

The *degenerative form* being pathognomonic of granular kidney deserves a little further consideration. It consists in the presence of small white glistening patches like crystals of cholesterin or the scales of a fish. These patches may be very tiny and require very careful searching for, but when found they are conclusive. They are patches of retinal degeneration and atrophy. In the most marked form they constitute the cart-wheel or spoke-like radiations round the yellow spot, but, of course, this is only an advanced condition. The spots are more interesting and important when they are few and tiny, for they may be accompanied by no defects of vision and be discovered only by routine ophthalmoscopic examination. They may be associated with hæmorrhages, but these present nothing characteristic.

The spots being patches of degeneration rarely, if ever, disappear. I used to say never, and practically this is really true; but if the renal condition improve they possibly may, and I think I have had one or two such cases under my own observation. What is very important is that they may be present and characteristic when the other signs of granular kidney may be open to question, so that they are of the greatest diagnostic importance.

Renal retinal degeneration is a late symptom or a sign of advanced disease. It used to be said that it meant that the patient had not more than two years to live. That is in a general way true when the degeneration is well marked, but it is not possible to say how long it had existed before it was looked for. I have seen the tiny spots long before any grave general symptoms appeared, and I have met with cases of advanced degeneration with much hæmorrhage which lasted to my knowledge five years and seven years respectively.

A year or two ago a gentleman, 40 years of age, was sent to me with the history that he was attacked with uræmic fits about six months previously, and on examination of the eye

advanced albuminuric degeneration with much hæmorrhage was discovered. A grave prognosis was given, with which I entirely agreed. I certainly thought the case almost hopeless, but I put him upon renal extract, which was steadily persevered with for many months. He gradually recovered and is now well. The fact of his complete recovery from the eye as well as the renal symptoms makes me feel some hesitation about the correctness of the diagnosis, but the condition seemed plain enough at the time, and no one who saw him when first ill, either physician or ophthalmologist, had any doubt. I have never seen any other case like it, and I record it for what it is worth.

Treatment.

I cannot at the end of such a paper as this go into the details of ordinary treatment, nor is it necessary when addressing an audience of practitioners. I will merely refer to a few points upon which an expression of opinion may be useful.

Of the causes of granular kidney we really know nothing. Many conditions to which it has been attributed—e.g., gout, lead, syphilis, and alcohol—though they may be contributory or aggravating, are certainly not prime causes. The disease is of such long duration and its commencement may be traced so far back in life that its beginnings elude our study. It is a very common disease now, but whether this means that it is increasing in frequency or only that it is more often diagnosed cannot be determined. One is tempted to believe that it is really on the increase, and to connect it with the strain and stress of modern life, for it is often met with in persons with a perfectly clean bill of health who have simply lived strenuous and anxious lives.

Granular kidney *in the early stage*, though capable of certain diagnosis, leads to no symptoms. The general health seems so good as to justify the patients in disbelieving the diagnosis and disregarding to their own detriment the advice based on it. At this stage treatment is precautionary and directed to obviate the risks to which the disease leads, of which the chief are cardiac failure, rupture of vessels, and nephritis; therefore, physical strain, exposure, and habits of excess, especially in diet and drink, should be avoided. The life led

should be of studied moderation in all things, of such a sort as would tend to keep the physical health at the highest level.

The risk at this stage is that the albuminuria which has been discovered should lead to its drastic treatment. The amount of albumin lost daily is too small to have of itself any effect upon the general health. Treatment has little or no effect in materially reducing its amount, still less in causing its disappearance, and drastic treatment by diet will injure the general health. Treat if need be, bnt do not over-treat.

There is another risk by no means negligible—viz., that of alarming the patient so much as to convert him into a renal hypochondriac whereby there is added to the renal disease, which is bad enough in itself, a neurotic condition of no slight gravity. To dwell too much upon the gravity of the case in the early stages to the patient is therefore undesirable, and, considering the long lease of life these early cases have, not warranted by facts.

When symptoms arise they must be treated on general principles, bearing in mind especially the nature of the disease which underlies them. Thus if cardiac symptoms develop over-stimulation must be avoided because of the increased blood pressure this would cause. For this reason digitalis is of doubtful value, and caffeine is a better remedy.

Vascular tension ought to be somewhat raised in granular kidney, and cannot be reduced much without detriment unless it be excessive. On the other hand, if the tension be low it must be raised, for with a low tension the patient is not so well, and will not be better until the tension has risen again. It is the tension that determines the use of digitalis. If the tension be raised it will do harm, but if low, and especially if associated with cardiac failure, digitalis is the best drug for the purpose. So soon, however, as the desired effect has been produced it should be suspended.

Hæmorrhage may not be serious except when it affects the brain. Fortunately, cerebral hæmorrhage rarely develops without some warning, and if the warning be taken may be avoided. These

warnings are often given by hæmorrhages elsewhere—e.g., into the conjunctiva or retina.

Epistaxis is common and may actually be useful, in so far as it may stave off a hæmorrhage into the brain. Epistaxis may be the first thing to bring the patient to the medical man. It may produce extreme exhaustion from which the health may never recover, so that the disease appears as if it dated from the epistaxis.

Hæmaturia is not uncommon and may lead to errors of diagnosis and treatment. Thus stone in the bladder may be wrongly diagnosed and operated for, or, if the hæmaturia be associated with cachexia, may raise the suspicion of malignant disease. As a rule, the hæmaturia is small in amount and does not require active treatment.

Generalised rushes are not uncommon in the later stages. They are generally more or less acute, toxic in origin, and of very grave prognosis. Acute general eruptions of any kind, if associated with albuminuria, are always serious, and if occurring in the course of granular kidney generally mark the beginning of the end.

For *sleeplessness* and *nervous restlessness* at night no sedative is better than cannabis indica, which in my experience is the great hypnotic in granular kidney. Opium and its preparations may be given if required without the risks once attributed to them.

Uræmia is often ushered in by headache, great restlessness, foul tongue with gastric and intestinal disturbances. I do not propose to enter into the question of the treatment of uræmia, except to say that it may often be staved off by active treatment if its imminence be recognised in time. For this purpose free purgation, active diaphoresis, and oxygen inhalation are of great use.

Of drugs there is none so good as pilocarpine, which in my experience is the great standby in granular kidney. It has been asserted that it is a risky drug to employ. That is not my experience. I have

used it largely for years with great benefit, and I have never seen any untoward effect produced by it.

Chronic Uræmia.

The symptoms which develop in the later stages of granular kidney are of a very miscellaneous character. They are accompanied by great impairment of the general health, and the asthenia and cachexia which result are often the most prominent features. This condition is often called chronic uræmia, but it is so different from acute uræmia that it is confusing to use the same name for both. *Chronic renal toxæmia* would be a better term.

Similar symptoms arise in chronic parenchymatous nephritis. They may rapidly develop in cases of suppression of urine; experimentally in animals where both ureters have been tied or both kidneys removed, or in man where both ureters have been accidentally ligatured, or one kidney has been removed, the other being absent or grossly diseased. as well as in some extreme cases of acute nephritis. A profound and rapidly progressive asthenia thus develops, generally without any fits or ordinary signs of acute uræmia; and of this the patient dies in about ten days or so without other obvious reasons except the asthenia.

Usually this condition is referred to poisoning by some substance which the kidneys ought normally to get rid of, but cannot. What the substance, or substances, may be no one knows, except that it certainly is not urea, as the name implies. There is, however, another alternative—viz., that the nutrition of the body suffers so profoundly for the want of some substance normally prepared by the kidney for use in the body—in other words, for the want of some internal secretion.

Renal Extract.

Has the kidney such an internal secretion? So far the pathologists have not been able to prove this experimentally. With their failure we must fall back on clinical evidence, in the hope that this may

show that chronic renal disease is favourably influenced by renal extract, just as myxœdema was proved to be by thyroid extract.

There is a difficulty unfortunately in preparing a reliable renal extract. I have tried various methods, and for a time used a glycerine extract. Messrs. Burroughs and Wellcome also attacked the problem, but without success, for they could get no preparation which was stable and could be preserved. I have consequently fallen back on an extract of kidney freshly prepared as required, using by preference the kidney of the pig as being a mixed feeder, rather than the kidney of a vegetable feeder like the sheep.

The great difficulty in obtaining evidence in favour of the usefulness of kidney extract in chronic renal disease lies in the fact that its use must be continued for weeks or months before results can be expected; generally patience is exhausted before the time required, and the treatment given up because signs of improvement are not immediate. Of course, in granular kidney the cases come under observation so late in the disease, when the mischief is so far advanced, that much benefit can hardly be looked for. Yet I have seen some of the symptoms, especially headaches, relieved by this means when they had resisted other treatment.

The most remarkable case I have met with is that which I referred to in passing when dealing with albuminuric retinitis. So extraordinary was this case that I must confess to the suspicion that the diagnosis of granular kidney must have been wrong. Still I felt quite certain of the diagnosis, as did the other medical men, when the case came first under observation.

Another remarkable case was as follows :—

The patient was a man, aged about 35, who had been attacked with acute nephritis some weeks previously. He had passed into the typical stage of chronic parenchymatous nephritis. He was passing a very large amount of albumin in the urine, was extremely anasarcous, with much ascites and a considerable pleuritic effusion on the right side. Both the abdomen and pleura had to be tapped more than once, but the fluid reaccumulated quickly. The man was sent into the hospital as a hopeless case. All the ordinary treatment was tried without success, the patient steadily

went downhill, and the prospect seemed desperate. Renal extract was now given night and morning. In a few days the patient volunteered the statement that "Dr. Reynolds' extract," as he called it, was doing him good, and that he felt ever so much better. The improvement soon became obvious, the effusions and the dropsy disappeared, slowly at first and then rapidly, and in about three wèeks had vanished. The albumin in the urine also rapidly decreased, and on leaving the hospital about six weeks later amounted to a mere trace. The man was carefully watched for some months. He went back to work and remained well.

I know there are rare instances in which rapid improvement in chronic parenchymatous nephritis occurs in what appear to be desperate cases. But I have never seen anything of this kind before, and I cannot avoid referring the result to the renal extract. In this view I was supported by those who had been watching the case with me.

My experience of some years now justifies me, I consider, in continuing and advocating the use of renal extract, but to be effectual in granular kidney it must be patiently and continuously persevered with for a long time.

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